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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,443	11/16/2001	Hyam I. Levitsky	213026	1421

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,443	LEVITSKY ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17-28,40-47 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,17-28,40-47 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on September 15, 2003 has been entered. Currently, claims 1-14, 17-28, 40-47, and 50-53 are pending and under examination. No claim has been amended.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1-14, 17-28, 40-47, and 50-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to the term "naturally" in the claim, applicants argue in 9/15/03 response, that the specification uses the term "naturally" as oppose to "modified", and acknowledge that the term is consistent with the meaning in the Standard English dictionary. Applicants disagree with the Office position that the loss of MHC expression as a result of a cancerous mutation is not considered "naturally" given its plain meaning, and allege that the basis of rejection is ill founded.

The arguments have been fully considered but they are not persuasive. This is because the court has clearly states, "WHERE APPLICANT ACTS AS HIS OR HER OWN LEXICOGRAPHER TO SPECIFICALLY DEFINE A TERM OF A CLAIM CONTRARY TO ITS ORDINARY MEANING, THE WRITTEN DESCRIPTION MUST CLEARLY REDEFINE THE CLAIM TERM AND SET FORTH THE UNCOMMON DEFINITION SO AS TO PUT ONE REASONABLY SKILLED IN THE ART ON NOTICE THAT THE APPLICANT INTENDED TO SO REDEFINE THAT CLAIM TERM. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999)" (emphasis added). Without clearly redefining the term that is contrary to or departs from its ordinary meaning, Applicants have not fulfilled the duty of putting one reasonably skilled on notice (see also the rejection of 35 USC § 112, 2nd paragraph). Accordingly, the rejection is well founded. If applicants intend to claim a cell line that lost the expression of MHC due to a cancerous mutation, the claims should clearly state so.

That said, an important reason that the term is rejected under Written Description is because the specification fails to properly disclose a species or the genus of the universal bystander cell lines that is truly "naturally lack" MHC class I and II antigens. As analyzed in the previous Office action, it appears that only red blood cells that do not have nuclei fit the category of "a universal bystander cell line", because they would naturally lack MHC-I and MHC-II antigens. The claims as they stand still encompassing a RBC. However, neither the art of record nor specification discloses a cell line of red blood cells. And since the red blood cells lacking a nucleus, it is unclear, if not unlikely, whether they could be modified to express an exogenous nucleic acid at levels >500-1000ng GM-CSF/106 cells/24 hours. Therefore, the specification fails to provide

sufficient description to convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants then argue that the written description guidelines and the *Amgen* case law does nothing to support the Office position because they are directed to a genus in which the species vary widely where the case at hand, the genus are all characterized by the same trait, i.e. (i) being a human cell line, (ii) naturally lacking MHC-I and MHC-II, (iii) being modified to express certain amount of GM-CSF.

The argument has been fully considered but found not persuasive. This is because there is no known red blood cell line (naturally lacking MHC expression) that meets the claim limitation, and if including the mutated tumor cell lines, there are thousands of cancerous cell lines widely varied in surface markers, such has been evidenced and discussed previously by the teachings of the skilled (such as *Klein et al, Wang et al, Ferrone et al, and Winchester et al*). Accordingly, by simply giving the characterized trait, one still can not predictably determine which cell line meets the claim limitation. Again, an adequate written description for a genus of cell lines that naturally lack MHC-I and MHC-II antigens requires more than a mere statement that it is part of the invention and reference to a potential method for identifying such; what is required is a description of the cell lines themselves. It is not sufficient to define the genus solely by its principal biological characterization, i.e. "**ANY human cell line that naturally lacks MHC-I and MHC-II antigens**", because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any cell line with that biological characteristics. Also, naming a type of material generically known to exist, in

the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all cell lines having a common trait without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). However the subject to be described is a chemical compound or a cell line or an animal, the general principle applies.

Applicants then argue that the identity of such cell line could be identified by searching the PubMed database for "HLA loss and tumors", and applicants need not describe that which is known in the art.

In response, a brief search of the suggested terms one would find 471 hits, which of them have lost expression of <u>both</u> MHC-I & -II are hard to search or yet to be determined. Since neither the instant disclosure nor the prior art of record teaches a cell line other than K562 that meets claim limitation, the following case law applies. The court states, "IN CHEMICAL CASE WHERE APPLICANT DISCLOSES THAT ONE SPECIES OF A CLASS OF CHEMICALS WILL ACCOMPLISH CERTAIN PURPOSE WITHOUT NAMING ANY OTHERS OF CLASS TO WHICH IT BELONGS OR WITHOUT SO DESCRIBING THE SPECIES AND ITS MODE OF OPERATION AS TO CALL ATTENTION TO FACT THAT OTHER MEMBERS OF CLASS ARE ITS EQUIVALENTS AND WILL PERFORM SAME FUNCTIONS, HE IS <u>NOT ENTITILED</u> TO BROADER SCOPE OF DISCLOSED INVENTION BY CLAIMING

WHOLE GROUP EVEN THOUGH THOSE SKILLED IN ART MAY KNOW THAT IN SOME RESPECTS AT LEAST DIFFERENT MEMBERS OF GROUP ARE EQUIVALENTS; CERTAIN MEMBERS OF WELL-DEFINED GROUP OF CHEMICALS MAY BE EQUIVALENTS FOR ONE PURPOSE AND NOT EQUIVALENT FOR ANOTHER. (*In re Soll*, 97 F.2d623, 38 USPQ 189 (CCPA 1938).

Therefore, for reasons of record and those set forth above, the instant specification fails to meet the written description requirement set forth under 35 U.S.C. §112, 1st paragraph.

ENABLEMENT REQUIREMENT

Claims 1-14, 17-28, 40-47, and 50-53 stand rejected under 35 U.S.C. 112, first paragraph, as containing subjection matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue in 9/15/03 response that whether the cell lines naturally lack MHCs could be readily obtainable or identified by appropriate antibodies, and referred to SK-MEL-33 and *Ferrone et al, Wang et al* as example of known cell lines. However, as discussed in the previous action, these cell lines are not lacking both MHC-I and MHC-II, they lack one or the other.

In this regard, the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement.

> However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, **undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.** It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added). In the instant case, except the K562 cell line, the specification fails to disclose another species of the genus, the skilled in the art intending to practice the invention has to first carry out undue experimentation to search for the cell lines that meet claim limitation.

With respect to the defined medium, applicants define the medium as any culture medium lacking a serum and submitted formula datasheet for commonly used basic culture media such as MEM and Ham's F-12. However, the claims encompass, and the illustrated embodiment is melanoma cells, and the art of record teaches that growing melanoma cells require the presence of an animal serum (*Winchester et al*, right column, page 6235). In view of such, the claims do not appear to be enabled in the absence of evidence to the contrary.

Accordingly, for reasons of record and those set forth above, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 17-22, 26, 27, 40-47, and 50-53 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Concerning the term, "naturally", Applicants acknowledge that its meaning is consistent with its plain meaning. However, they further consider that cell lines that lost MHC expression due to cancerous mutation are included in the category. In this regard, the claims are vague and indefinite because where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "naturally" in claims is used by the claim to encompass "mutations", while the accepted meaning is "by nature or inherent". It is noted when the cell mutated, it has changed its natural form. The term is indefinite because the specification does not clearly redefine the term.

Applicants consider claim 2 was rejected because it uses "and" twice. This is not the case. Claim 2 is rejected because it is unclear whether "the receptors for EBV" following the second "and" is required to be absent, thus, the metes and bounds of the claim is unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50, and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Dranoff et al* (US 5,637,483, IDS/AB), in view of *Ferrone et al* (Immunol Today 1995;16:487-94), and as evidenced by *Thomas et al* (Human Gene Ther 1998 Apr;9:835-43).

In 9/15/03 response, Applicants argue that none of the reference teach a universal bystander cell line, or appreciate the importance of using a cell line that naturally lacks MHC-I and MHC-II. Applicants also argue that there is no motivation to combine references, since reference teaches an allogenic MHC can enhance the induction of systemic antitumor immunity.

The arguments have been fully considered but they are not persuasive. This is because the references are combined to show that one of skilled in the art knows modifying tumor cells with GM-CSF would enhance anti-tumor immunity, and there is motivation to modify different types of tumor cells with GM-CSF, and one line of tumor

cells modified may actually lacks both MHC-I and MHC-II. Here, the motivation is not whether the skilled in the art appreciate the importance of using a cell line lacking both MHC-I and MHC-II, the motivation required is whether the ordinary skilled would be motivated to modify different types of tumor cells.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Dandroff et al,* by substituting the B16 melanoma cells with the tumor cell line of interest with a reasonable expectation of success, and one of the tumor cell lines modified would intrinsically lacking both MHC-I and -II as taught by *Ferrone et al* (see Office action dated 4/12/03, page 12, 2nd & 3rd paragraphs). The ordinary skilled artisan would have been motivated to modify the claimed invention by using different types of melanoma cells according to the type of melanoma the individual is suffering, because GM-CSF modified melanoma cells could trigger or enhance antitumor immunity in the recipient that often lacks efficient anti-tumor cellular activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 5, 7, 11, 17, 20, 22-24, 28, 40, 41, 44, 45, 50, and 52 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Dranoff et al* (US 5,637,483, IDS/AB), and *Ferrone et al* (Immunol Today 1995;16:487-94) as applied to claims 1, 5, 7, 17, 20, 22, 28, 40, 41, 44, 45, 50, and 52 above, and further in view of *Shepard et al* (US 6,348,352) or *Polack et al* (US 6,521,449).

Applicants presented the same arguments with respect to Dranoff and Ferrone, and further argue that neither Shepard nor Polack cures the deficiencies of Dranoff and Ferrone.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, it is the combined references as a whole that teach the claimed invention. The arguments toward the teaching of Dranoff and Ferrone have been addressed above and will not be reiterated.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-14, 17-28, 40-47, and 50-53 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-21

of U.S. Patent No. 6,464,973. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims encompass the claims of the cited patent.

Applicants indicated that upon an indication of allowable subject matter, a terminal disclaimer will be submitted.

Until then, the rejection stands.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
December 15, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER